Overview of the Above Amendments

Claims 1-6 have been amended to claim the subject invention with greater particularity. Specifically, claims 1-6 all recite that the nucleic acid molecule encodes "an immunogenic polypeptide" with at least "90% sequence identity" to the specified "contiguous" amino acid sequence. Additionally, the term "about" has been deleted from the claims. Support for these amendments may be found throughout the specification at, e.g., page 9, lines 17-20; and page 16, lines 16-21.

New claims 44-55 have been added. Claim 44 recites that the nucleic acid molecule comprises a sequence selected from the group consisting of: (a) a sequence encoding the contiguous amino acid sequence shown at positions 1 through 256, inclusive, of Figures 4A-4C (SEQ ID NO:2); and (b) a sequence encoding the contiguous amino acid sequence shown at positions 29 through 256, inclusive, of Figures 4A-4C (SEQ ID NO:2). Claims 45 and 46 pertain to the individual members of the Markush group recited in claim 44. Claims 47-49 pertain to recombinant vectors and depend from claims 44-46. Claims 50-52 recite host cells transformed with the recombinant vectors and claims 53-55 relate to methods of recombinant production using the host cells. Support for these claims can be found in the claims as originally filed, as well as throughout the specification at, e.g., page 18, lines 20-28; pages 22-26; and in the examples. A copy of the currently pending claims, incorporating the amendments made herein, is appended for the Examiner's convenience.

35 U.S.C. §112, Second Paragraph

Claims 1-12 stand rejected under 35 U.S.C. § 112, second paragraph as allegedly indefinite. In particular, The Office objects to the use of the phrase "at least about" in the claims. This terminology has been deleted. The Office also asserted the use of the phrase "the nucleotide sequence shown at positions 157 through 924" and "241 through 924" was unclear. Applicants respectfully disagree. Nevertheless, this terminology has been canceled and the current claims are framed with reference to the "contiguous" sequence occurring at specified positions.

Accordingly, withdrawal of the rejections under 35 U.S.C. §112, second paragraph is respectfully requested.

Utility

The Office rejected claims 1-12 under 35 U.S.C. §101 and 35 U.S.C. §112, first paragraph, alleging "the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility." Office Action, page 3. The Office argues:

> The claims encompass any randomly truncated nucleotide molecule with the recited degree of change of SEQ ID NO:1. However, the specification is limited to the nucleic acid sequence of SEQ ID NO:1 which encodes the polypeptide of SEQ ID NO:2, a Streptococcus uberis CAMP factor. The specification only states that DNA sequence homology can be determined by hybridization of polynucleotide (page 16). The claimed nucleic acid molecule is not supported by either a specific and substantial asserted utility or a well established utility because the specification fails to assert any utility for the nucleic acid molecule and neither the specification as filed nor any art of record disclose or suggest any activity for the claimed nucleic acid molecule such that any utility would be well established for the nucleic acid molecule.

Office Action, page 4. However, applicants respectfully disagree.

In particular, the new Examiner Guidelines on the utility requirement provide for

three basic utility criteria -- (1) specific, (2) substantial and (3) credible.. The above statement implies the Examiner believes applicants' utility is credible as credibility was not challenged. Applicants assert that the utility presented in the instant specification is also specific and substantial.

The Utility Guidelines require that only one credible utility need be disclosed in the application. If the applicant has asserted that the claimed invention is useful for any particular practical purpose and the assertion would be considered credible by a person of ordinary skill in the art, a rejection based on lack of utility is improper. Applicants have complied with these standards.

Applicants have specified throughout the application that the immunogenic proteins encoded by the claimed nucleic acid molecules, including those encoding the amino acid sequences found at positions 1-256 and 29-256 of Figures 4A-4C (SEQ ID NO:2), as well as immunogenic sequences with homology thereto, are useful for the treatment of bacterial infections, particularly, the specific disorder of mastitis. See, e.g., page 4, lines 14-22; pages 19-20, bridging paragraph. Moreover, *in vivo* data is presented in Example 6 of the application, showing that a representative molecule encoded by the claimed nucleic acid sequence, was immunogenic (see, Tables 2 and 3) and indeed prevented mastitis (see, Table 4). It is clear that applicants have explicitly set forth a specific and substantial utility, namely, the treatment of mastitis, for the molecules of the subject invention and that this utility would be considered credible, based on the actual data presented in the application. Applicants need not resort to a demonstration of "well established" utility for the claimed molecules as they have made an adequate showing in the application as filed. Applicants note that the present claims are not directed to ESTs, i.e., molecules that may have no known function, but rather to nucleic acid molecules that encode immunogenic proteins that have been shown by applicants to function in the treatment of mastitis.

Moreover, contrary to the Office's statements, applicants have also explained that homology can be determined, e.g., by a comparison of sequences using readily available computer programs, such as ALIGN. See, page 16, lines 5-11 of the application.

Based on the foregoing, applicants respectfully submit that the application complies with the utility requirements of 35 U.S.C. §101 and §112, first paragraph and that this basis for rejection should be withdrawn.

Enablement

The Office also rejected claims 1-12, under 35 U.S.C. §112, first paragraph, as nonenabled. The Office asserts:

> The specification fails to provide characteristics of any nucleic acid molecule with a recited degree of change which will encode the polypeptide variants of the SEQ ID NO:2 with the function a Streptococcus uberis CAMP factor. The specification fails to teach what the critical portions of SEQ ID NO:1 are needed for encoding polypeptide variants of SEQ ID NO:2 with activity. Protein chemistry is probably one of the most unpredictable areas of biotechnology and the art teaches that the significance of any particular amino acid and sequences for different aspects of biological activity can not be predicted a priori and must be determined empirically on a case by case basis.

Office Action, page 5. In support of these allegations, the Office cites excerpts from a 1976 edition of "Peptide Hormones." Applicants submit that the Office's reliance on a reference that published at least 19 years prior to applicants' priority date is wholly improper as the standard for enablement is judged with respect to the time the application in question is filed.

Moreover, the "Peptide Hormone" reference proffered as evidence of the state of the art is inapplicable in the present case. Applicants do not deny that the interaction of a hormone with its receptor is a complicated process and that it may be difficult to predict which portions of a peptide hormone are necessary to ensure the proper biological effect. However, the present claims not directed to hormones or molecules involved in signaling

pathways! Rather, applicants' claims pertain to nucleic acid sequences that encode immunogenic proteins. Thus, the cited reference is not an appropriate indicator regarding the state of the art of immunization at the time the present application was filed. The Office has failed to provide proper reasoning for doubting the objective truth of the statements relied upon in the application for enabling support. See, *In re Marzocchi*, 169 USPQ 367 (CCPA 1971). Thus, the Office has failed to provide a *prima facie* case of nonenablement.

Moreover, the Office's assertions suggest that the Examiner misunderstands what is necessary to satisfy the enablement requirement in this context. Specifically, it suggests that the Examiner has found the enablement requirement unsatisfied with respect to immunogenic polypeptides with at least 90% sequence identity to SEQ ID NO:2 because applicants have provided experimental data only for the protein of SEQ ID NO:2.

The Examiner is incorrect. As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of § 112 is satisfied. *In re Fisher,* 166 USPQ 18, 24 (CCPA 1970). Applicants are not obligated to provide experimental data in order to enable their claimed invention.

Perhaps the Office misunderstands applicants' invention. In particular, the invention is directed to nucleic acid molecules which encode "immunogenic" polypeptides. Applicants' invention does not require nucleic acid molecules that encode a "biologically active" CAMP factor i.e., one displaying CAMP cytolytic activity. Indeed, such cytolytic activity is toxic and undesirable. See, e.g., paragraph 5 of the Declaration of Andrew A. Potter, Ph.D. ("the Declaration"), submitted in USSN 08/658,277, now issued as U.S. Patent No. 5,863,543, the parent of the present divisional application. A copy of the Declaration accompanies this amendment for the Examiner's convenience. Thus, the Office's concern with preserving the biological activity of the CAMP factor is in error.

Rather, applicants' concern is only with providing nucleic acid molecules that encode immunogenic (e.g., epitope-containing) polypeptides of SEQ ID NO:2. Epitopes contained within the immunogenic polypeptides need not be conformational, as evidenced by the fact that the CAMP factor polypeptide used in the examples does not retain its native conformation since it has been denatured and no refolding step is employed prior to use. Applicants submit, therefore, that one of skill in the art would not find it unduly burdensome to identify immunogenic polypeptides containing linear epitopes with 90% or more sequence identity to the amino acid sequence of SEQ ID NO:2. Techniques for doing so are discussed in the patent application at page 13, lines 10-20. Applicants therein explain that immunogenic CAMP factor polypeptides can be rapidly and readily identified using, e.g., techniques described in issued U.S. Patent No. 4,708,871. The method detailed in the '871 patent involves concurrently synthesizing large numbers of peptides on solid supports, the peptides corresponding to portions of the protein molecule, and reacting the peptides with antibodies while the peptides are still attached to the supports. These methods can easily be used to identify immunogenic polypeptides derived from the *S. uberis* CAMP factor protein without undue experimentation. The Office is reminded that even a large amount of experimentation is permitted under §112, first paragraph, provided it is routine. *Ex parte Jackson*, 217 USPQ 804, 807 (Bd. App. 1982) (a claim is acceptable under §112 even if it requires extensive experimentation, as long as the experimentation is routine).

Applicants submit that they have indeed complied with the enablement requirement of 35 U.S.C. §112, first paragraph. Routine methods for mapping epitopes were known to those of skill in the art at the time the application was filed and are taught in the specification. Applicants submit that, given the level of skill in the art, the description in the specification and the particular examples, a skilled artisan could readily practice the claimed invention without undue experimentation.

Moreover, it is Applicants' understanding after attending the Group 1600 Open House October, 2000, that including a recitation of structure (*e.g.*, percent identity with reference to SEQ ID NO:2) and function (*e.g.*, immunogenicity) will generally render a claim acceptable under 35 U.S.C. § 112, first paragraph. Therefore, without acquiescing in the rejection and in an effort to further prosecution, applicants have amended the claims to further include structure and function limitations.

Hence, applicants believe that the preceding arguments and amendments overcome the Examiner's rejections under § 112, first paragraph with respect to the enablement requirement, and therefore request that the rejection be withdrawn.

Written Description

Claims 1-12 stand rejected under 35 U.S.C. § 112, first paragraph based on the written description requirement. The Office alleges that the specification as filed fails to provide support for "the nucleotide sequence shown at positions 157-924 of SEQ ID NO:1 and the nucleotide sequence shown at positions 241-924 of SEQ ID NO:1." Office Action, page 6. Applicants respectfully disagree. In particular, as explained in the previous amendment, these DNA positions correspond to amino acid positions 1-256 and 29-256, respectively, of SEQ ID NO:2. See, for example, page 18, lines 20-28 with reference to Figures 4A-4C. Further support for the recitations may be found at page 18, lines 13-15 and page 41, lines 22-26. Thus, explicit support for the recitations is indeed present.

Notwithstanding the above, and without acquiescing in this rejection, the current claims are framed with reference to the amino acid sequences encoded by the nucleic acid molecules. Thus, this basis for rejection has been rendered moot and withdrawal thereof is respectfully requested.

35 U.S.C. § 102

Claims 1-3 were rejected under 102(b) as allegedly anticipated by Podblielski, *Med Microbiol Immunol* (1994) 183:239-256 ("Podblielski"). The Office argues that "claims 1-3 read on an isolated nucleic acid molecule with any length (e.g., a single nucleic acid)" and that "Podblielski teaches an isolated nucleic acid molecule encoding group B *Streptococcus* CAMP factor comprising a sequence having 100% identity to various positions of 157 through 924 and 241 through 924 of SEQ ID NO:1." Office Action, page 7. Applicants respectfully disagree.

In particular, applicants submit that the previous claims clearly pertained to a contiguous sequence of nucleotides and did not relate to a nucleotide sequence of any size within positions 157/241 to 924. Nevertheless, in an effort to advance prosecution, applicants have inserted the term "contiguous" into the claims. Applicants note that the search results provided by the Patent Office show only 64.9% sequence identity between Podblielski and applicants' sequence. Accordingly, this basis for rejection has been overcome and withdrawal thereof is respectfully requested.

35 U.S.C.§ 103(a)

Claims 1-12 were rejected as allegedly unpatentable over Podblielski as applied to claims 1-3, and Sambrook et al., *Molecular Cloning, A Laboratory Manual* Chapter 17, Expression of Cloned Genes in *Escherichia coli* ("Sambrook").

The Office alleges that Podblielski teaches a sequence "having 100% identity to various positions of 157 through 924 and 241 through 924 of SEQ ID NO:1" Office Action, page 8. The Office acknowledges that Podblielski "does not teach inserting the cloned gene into an expression vector" (Office Action, page 8) but cites Sambrook as teaching standard methods for expression of cloned genes. Thus, the Office concludes "it would be *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to insert the cloned gene of Podblielski into a recombinant vector..."

Office Action, page 8. However, applicants respectfully disagree that the combination renders the present claims obvious.

It is well settled that the Examiner bears the burden of establishing a *prima facie* case of obviousness. *See, e.g., In re Ryckaert,* 28 USPQ2d 1955, 1956 (Fed. Cir. 1993); and *In re Oetiker,* 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). It is also well established that the Examiner may not combine references to create an obviousness rejection unless there is some suggestion or motivation in the prior art to make the combination. *See, e.g., Arkie Lures, Inc. v. Gene Larew Tackle, Inc.,* 43 USPQ2d 1294 (Fed. Cir. 1997); *In re Oetiker, supra.* Applicants submit that the Examiner has failed to establish a *prima facie* case of obviousness over the cited combination.

First of all, Podblielski's sequences are all derived from either of *Streptococcus agalactiae* or *Stahpylococcus aureus* and not *S. uberis*. In fact, *S. uberis* is not even mentioned in Podblielski. To the best of applicants' knowledge, no one had cloned and expressed CAMP factor proteins from *S. uberis* prior to the present invention. Moreover, at the time the application was filed, there was no indication in the art that CAMP factor could be used to raise an immunogenic response useful in the treatment of mastitis. In fact, one of skill in the art would not be motivated to use CAMP factor or proteins derived therefrom for eliciting an immune response. As explained in paragraphs 6 and 7 of the accompanying Declaration, this actually goes against the conventional wisdom in the art at the time the application was filed. Particularly, as explained in Exhibit B which accompanies the Declaration, invasion of the mammary gland by Streptococcal bacteria results in an inflammatory response which increases the somatic cell count, a criterium by which clinical mastitis is measured. However, the inflammatory response is also the basic mechanism by which an organism protects itself against disease. Therefore, the very act of immunization would logically lead to enhanced somatic cell counts and, by definition, constitute mastitis. The authors, at page 417, last sentence of the first full paragraph, state: "It seems unlikely, therefore, that a protective mechanism can be

developed which depended only on specific antibacterial antibody, even if that antibody could be transported across an intact secretory epithelium." In the last sentence of the paper the authors state: "Only when protection can be achieved by eliciting an inflammatory response which is insufficient to constitute subclinical mastitis, will immunization against bovine mastitis have succeeded."

Based on the foregoing, it is apparent that one of skill in the art would not be motivated to obtain nucleic acid sequences encoding immunogenic CAMP factor proteins as claimed.

Sambrook fails to provide the missing link. Sambrook pertains generally to the field of gene expression, does not in anyway pertain to *S. uberis*, let alone *S. uberis* CAMP factor, and therefore does not further elucidate nucleic acid molecules encoding immunogenic CAMP factor polypeptides as claimed. As explained above, it is believed that prior to applicants' invention, no one had cloned and expressed CAMP factor proteins from *S. uberis*. Accordingly, applicants submit that the Office has failed to present a *prima facie* case of obviousness and that this basis for rejection should be withdrawn.

III. CONCLUSION

Applicants respectfully submit that the claims are novel and nonobvious over the art and comply with the requirements of 35 U.S.C. §101 and 35 U.S.C. §112. Accordingly, allowance is believed to be in order and an early notification to that effect would be appreciated.

If the Examiner notes any further matters which he believes may be expedited by a telephone interview, he is requested to contact the undersigned attorney at (650) 325-7812.

Respectfully submitted,

Date: 7/17/01 By: _____

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MARKED-UP CLAIMS (USSN 09/234,733; 9000-0030.10)

1. (Three times amended) An isolated nucleic acid molecule consisting of a sequence selected from the group consisting of: (a) a sequence encoding an immunogenic polypeptide having at least [about 80%] 90% sequence identity to the [nucleotide] contiguous amino acid sequence shown at positions [157 through 924] 1 through 256, inclusive, of Figures 4A-4C (SEQ ID NO:[1]2); and (b) a sequence encoding an [amino acid sequence] immunogenic polypeptide having at least [about 80%] 90% sequence identity to the [nucleotide] contiguous amino acid sequence shown at positions [241 through 924] 29 through 256, inclusive, of Figures 4A-4C (SEQ ID NO:[1]2).

2. (Four times amended) The nucleic acid molecule of claim 1 wherein said nucleic acid molecule encodes an immunogenic polypeptide having a sequence [has] with at least [about] 90% sequence identity to the [nucleotide] contiguous amino acid sequence shown at positions [157 through 924] 1 through 256, inclusive, of Figures 4A-4C (SEQ ID NO:[1]2).

3. (Three times amended) The nucleic acid molecule of claim 1 wherein said nucleic acid molecule encodes an immunogenic polypeptide having a sequence [has] with at least [about] 90% sequence identity to the [nucleotide] contiguous amino acid sequence shown at positions [241 through 924] 29 through 256, inclusive, of Figures 4A-4C (SEQ ID NO:[1]2).

4. (Three times amended) A recombinant vector comprising:

(a) a nucleic acid molecule encoding an immunogenic polypeptide comprising a sequence selected from the group consisting of: (i) a sequence having at least [about 80%] 90% sequence identity to the [nucleotide] contiguous amino acid sequence shown at positions [157 through 924] 1 through 256, inclusive, of Figures 4A-4C (SEQ ID NO:[1]2); and (ii) a sequence having at least [about 80%] 90% sequence identity to the [nucleotide] contiguous amino acid sequence shown at positions [241 through 924] 29 through 256, inclusive, of Figures 4A-4C (SEQ ID NO:[1]2); and

(b) control elements that are operably linked to said nucleic acid molecule whereby said

coding sequence can be transcribed and translated in a host cell, and at least one of said control elements is heterologous to said coding sequence.

5. (Three times amended) A recombinant vector according to claim 4, wherein said nucleic acid molecule encodes an immunogenic polypeptide which comprises a sequence having at least [about] 90% sequence identity to the [nucleotide] contiguous amino acid sequence shown at positions [157 through 924] 1 through 256, inclusive, of Figures 4A-4C (SEQ ID NO:[1]2).

6. (Three times amended) A recombinant vector according to claim 4, wherein said nucleic acid molecule encodes an immunogenic polypeptide which comprises a sequence having at least [about] 90% sequence identity to the [nucleotide] contiguous amino acid sequence shown at positions [241 through 924] 29 through 256, inclusive, of Figures 4A-4C (SEQ ID NO:[1]2).

--44. (New) An isolated nucleic acid molecule comprising a sequence selected from the group consisting of: (a) a sequence encoding the contiguous amino acid sequence shown at positions 1 through 256, inclusive, of Figures 4A-4C (SEQ ID NO:2); and (b) a sequence encoding the contiguous amino acid sequence shown at positions 29 through 256, inclusive, of Figures 4A-4C (SEQ ID NO:2).

45. (New) The nucleic acid molecule of claim 44 wherein said sequence encodes the contiguous amino acid sequence shown at positions 1 through 256, inclusive, of Figures 4A-4C (SEQ ID NO:2).

46. (New) The nucleic acid molecule of claim 44 wherein said sequence encodes the contiguous amino acid sequence shown at positions 29 through 256, inclusive, of Figures 4A-4C (SEQ ID NO:2).

47. (New) A recombinant vector comprising:

(a) a nucleic acid molecule according to claim 44; and

(b) control elements that are operably linked to said nucleic acid molecule whereby said

coding sequence can be transcribed and translated in a host cell, and at least one of said control elements is heterologous to said coding sequence.

48. (New) A recombinant vector comprising:

(a) a nucleic acid molecule according to claim 45; and

(b) control elements that are operably linked to said nucleic acid molecule whereby said coding sequence can be transcribed and translated in a host cell, and at least one of said control elements is heterologous to said coding sequence.

49. (New) A recombinant vector comprising:

(a) a nucleic acid molecule according to claim 46; and

(b) control elements that are operably linked to said nucleic acid molecule whereby said coding sequence can be transcribed and translated in a host cell, and at least one of said control elements is heterologous to said coding sequence.

50. (New) A host cell transformed with the recombinant vector of claim 47.

51. (New) A host cell transformed with the recombinant vector of claim 48.

52. (New) A host cell transformed with the recombinant vector of claim 49.

53. (New) A method of producing a recombinant CAMP factor comprising:

(a) providing a population of host cells according to claim 50; and

(b) culturing said population of cells under conditions whereby the CAMP factor encoded by the coding sequence present in said recombinant vector is expressed.

54. (New) A method of producing a recombinant CAMP factor comprising:

(a) providing a population of host cells according to claim 51; and

(b) culturing said population of cells under conditions whereby the CAMP factor encoded by the coding sequence present in said recombinant vector is expressed.

55. (New) A method of producing a recombinant CAMP factor comprising:

(a) providing a population of host cells according to claim 52; and

(b) culturing said population of cells under conditions whereby the CAMP factor encoded by the coding sequence present in said recombinant vector is expressed.--